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Health Effects Assessment for Mirex

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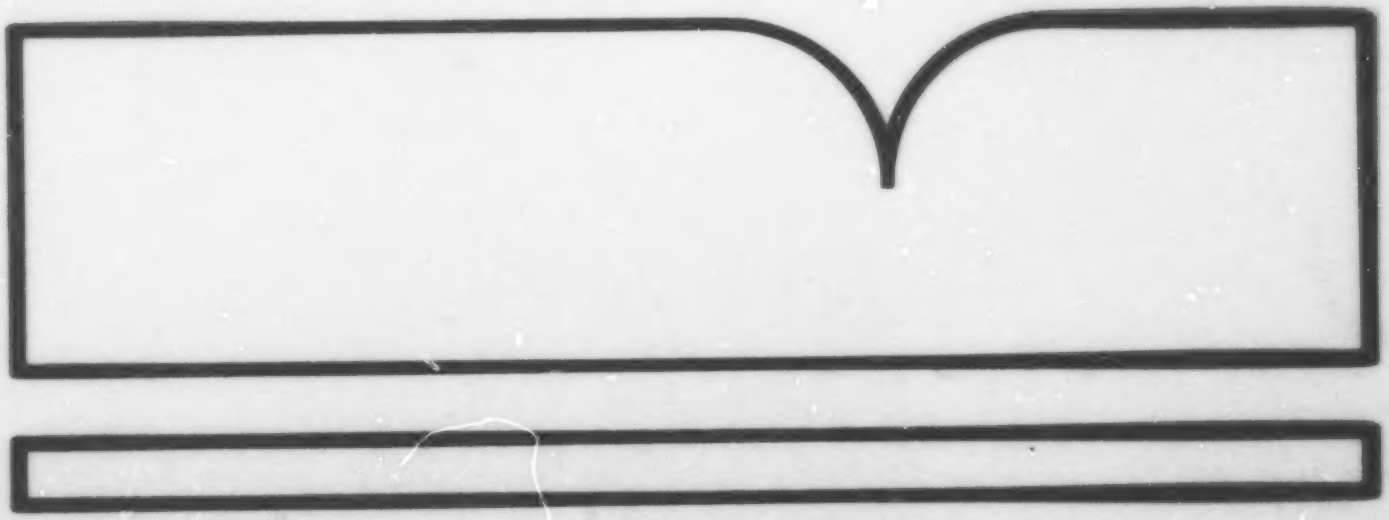

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HEALTH EFFECTS ASSESSMENT FOR MIREX

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16. ABSTRACT

This report summarizes and evaluates information relevant to a preliminary interim assessment of adverse health effects associated with specific chemicals or compounds. The Office of Emergency and Remedial Response (Superfund) uses these documents in preparing cost-benefit analyses under Executive Order 12991 for decision-making under CERCLA. All estimates of acceptable intakes and carcinogenic potency presented in this document should be considered as preliminary and reflect limited resources allocated to this project. The intent in these assessments is to suggest acceptable exposure levels whenever sufficient data are available. The interim values presented reflect the relative degree of hazard associated with exposure or risk to the chemical(s) addressed. Whenever possible, two categories of values have been estimated for systemic toxicants (toxicants for which cancer is not the endpoint of concern). The first, RfD_S or subchronic reference dose, is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs during a limited time interval. The RfD is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs for a significant portion of the lifespan. For compounds for which there is sufficient evidence of carcinogenicity, q_1^*s have been computed, if appropriate, based on oral and inhalation data if available.

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PREFACE

The report summarizes and evaluates information relevant to a preliminary interim assessment of adverse health effects associated with mirex. All estimates of acceptable intakes and carcinogenic potency presented in this document should be considered as preliminary and reflect limited resources allocated to this project. Pertinent toxicologic and environmental data were located through on-line literature searches of the TOXLINE and the CHEMFATE/DATALOG data bases. The basic literature searched supporting this document is current up to May, 1986. Secondary sources of information have also been relied upon in the preparation of this report

The intent in these assessments is to suggest acceptable exposure levels whenever sufficient data were available. Values were not derived or larger uncertainty factors were employed when the variable data were limited in scope tending to generate conservative (i.e., protective) estimates. Nevertheless, the interim values presented reflect the relative degree of hazard associated with exposure or risk to the chemical(s) addressed.

Whenever possible, two categories of values have been estimated for systemic toxicants (toxicants for which cancer is not the endpoint of concern). The first, the AIS or acceptable intake subchronic, is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs during a limited time interval (i.e., for an interval that does not constitute a significant portion of the lifespan). This type of exposure estimate has not been extensively used or rigorously defined, as previous risk assessment efforts have been primarily directed toward exposures from toxicants in ambient air or water where lifetime exposure is assumed. Animal data used for AIS estimates generally include exposures with durations of 30-90 days. Subchronic human data are rarely available. Reported exposures are usually from chronic occupational exposure situations or from reports of acute accidental exposure.

The AIC, acceptable intake chronic, is similar in concept to the ADI (acceptable daily intake). It is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs for a significant portion of the lifespan [see U.S. EPA (1980) for a discussion of this concept]. The AIC is route-specific and estimates acceptable exposure for a given route with the implicit assumption that exposure by other routes is insignificant.

Composite scores (CSs) for noncarcinogens have also been calculated where data permitted. These values are used for ranking reportable quantities; the methodology for their development is explained in U.S. EPA (1983b).

For compounds for which there is sufficient evidence of carcinogenicity, AIS and AIC values are not derived. For a discussion of risk assessment methodology for carcinogens refer to U.S. EPA (1980). Since cancer is a process that is not characterized by a threshold, <u>any</u> exposure contributes an increment of risk. Consequently, derivation of AIS and AIC values would be inappropriate. For carcinogens, q_1^*s have been computed based on oral and inhalation data if available.

ABSTRACT

In order to place the risk assessment evaluation in proper context, refer to the preface of this document. The preface outlines limitations applicable to all documents of this series as well as the appropriate interpretation and use of the quantitative estimates presented.

The database for mirex is extensive and includes subchronic and chronic toxicity studies, teratogenicity/reproductive effects studies, and three carcinogenicity studies on rats and mice. The carcinogenicity studies provide the basis for the mirex risk assessment; all three studies indicated that mirex is associated with an increased incidence of liver tumors in rats and mice. Results from a draft NTP (1987) bioassay report were considered to be most useful for quantitative risk assessment. In this study, mirex caused a dose-related increase in liver neoplastic nodules and adrenal pheochromocytomas in male F344/N rats receiving 0, 0.1, 1, 10, 25 or 50 ppm mirex in the diet for 104 weeks. Female rats exposed to the same dietary concentrations showed dose-related increases in leukemia. Control incidences of liver neoplastic nodules were elevated when compared with historical controls. In a second study with female rats using dietary concentrations of 0, 50 or 100 ppm, the dose-related increase in leukemia was reproduced and a dose-related increase in incidence of neoplastic nodules was also reported.

A human carcinogenic potency estimate (q_1^*) for oral exposure of 1.8 $(mg/kg/day)^{-1}$ is chosen to reflect the potency of mirex. This value is based upon pooled incidence of adrenal pheochromocytomas, neoplastic nodules and hepatocellular carcinomas in male rats. Data were insufficient for derivation of a carcinogenic potency estimate for inhalation exposure.

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TABLE OF CONTENTS

		Page
1.	ENVIRONMENTAL CHEMISTRY AND FATE	1
2.	ABSORPTION FACTORS IN HUMANS AND EXPERIMENTAL ANIMALS	3
2.1.	ORAL	3
2.2.	INHALATION	3
3.	TOXICITY IN HUMANS AND EXPERIMENTAL ANIMALS	4
3.1.	SUBCHRONIC	4
3.1.1.	Oral	4
3.1.2.	Inhalation	4
3.2.	CHRONIC	4
3.2.1.	Oral	4
3.2.2.	Inhalation	8
3.3.	TERATOGENICITY AND OTHER REPRODUCTIVE EFFECTS	8
3.3.1.	Oral	8
3.3.2.	Inhalation	12
3.4.	TOXICANT INTERACTIONS	12
4.	CARCINOGENICITY	13
4.1.	HUMAN DATA	13
4.2.	BIOASSAYS	13
4.2.1.	Oral	13
4.2.2.	Inhalation	19
4.3.	OTHER RELEVANT DATA	20
4.4.	WEIGHT OF EVIDENCE	20
5.	REGULATORY STANDARDS AND CRITERIA	21
6.	RISK ASSESSMENT	22
6.1.	ACCEPTABLE INTAKE SUBCHRONIC (AIS)	22
6.2.	ACCEPTABLE INTAKE CHRONIC (AIC)	22
6.3.	CARCINOGENIC POTENCY (q_1^*)	22
6.3.1.	Oral	22
6.3.2.	Inhalation	28
7.	REFERENCES	29
APPENDIX:	Summary Table for Mirex	39

LIST OF TABLES

No.	Title	Page
1-1	Selected Physical and Chemical Properties and Half-Lives for Mirex	2
3-1	Summary of Subchronic Oral Toxicity Data for Mirex.	6
3-2	Summary Table for Teratogenicity and Other Reproductive Effects	9
4-1	Summary Table for Carcinogenicity Studies on Mirex.	14
6-1	Cancer Data Sheet for Derivation of q_1^*	24
6-2	Cancer Data Sheet for Derivation of q_1^*	25
6-3	Cancer Data Sheet for Derivation of q_1^*	26

LIST OF ABBREVIATIONS

ADI	Acceptable daily intake
AIC	Acceptable intake chronic
AIS	Acceptable intake subchronic
LD_{50}	Dose lethal to 50% of recipients
MTD	Maximum tolerated dose
NOEL	No-observed-effect level
PCB	Polychlorinated biphenyl
ppm	Parts per million

1. ENVIRONMENTAL CHEMISTRY AND FATE

Selected chemical and physical properties and environmental fate of mirex are presented in Table 1-1.

Experimental evidence suggests that mirex is one of the most stable organochlorine compounds investigated to date. It is resistant to physical, chemical and biological degradation (U.S. EPA, 1978). The half-life of mirex in air could not be located in the available literature. In the atmosphere, mirex is expected to exist primarily as adsorbed matter on airborne particulates because of its low vapor pressure. Its resistance to chemical and photochemical reactions indicates that long distance transport may occur before removal by dry or wet deposition. In water, mirex is expected to bioaccumulate in aquatic organisms and strongly adsorb to suspended solids and sediments. It is generally agreed that mirex is transported in water adsorbed to organic particulates. Thus, its movement would be expected to follow water currents. Patterns of occurrence in sediments of Lake Ontario support this conclusion (EHD, 1977).

Mirex will exist predominantly in the sediments of surface water, adsorbed to particulate matter or dissolved in aliphatic materials (NAS/NRC, 1978).

Bomberger et al. (1983) reported that mirex does not leach into the soil profile and it volatilizes slowly. Since the compound is strongly adsorbed to soil and remains on the surface, a major loss from terrestrial systems is expected to be erosion and transport into surface waters. Its estimated half-life in soil is >12 years (NAS/NRC, 1978).

TABLE 1-1

Selected Physical and Chemical Properties and Half-Lives for Mirex

Property	Value	Reference
CAS number:	2385-85-5	
Chemical class:	organochlorine pesticide	
Molecular weight:	545.5	
Vapor pressure at 25°C:	3×10^{-7} mm Hg	IARC, 1979
Water solubility at 22°C:	0.07 µg/ℓ	Reinbold et al., 1979
Log octanol/water partition coefficient:	6.89	Veith et al., 1979
Bioconcentration factor:	18,200 fathead minnow (Pimephales promelas)	Veith et al., 1979
Log soil adsorption coefficient:	5.38	Reinbold et al., 1979
Environmental half-life:	5-12 years	NAS/NRC, 1978
Half-life in Soil	>12 years	NAS/NRC, 1978

NA = Not available

2. ABSORPTION FACTORS IN HUMANS AND EXPERIMENTAL ANIMALS

2.1. ORAL

Mehendale et al. (1972) administered oral doses of 6 mg/kg to rats and found that ~60% of the dose was recovered in feces within 48 hours, probably representing unabsorbed mirex. After this, excretion leveled off, suggesting that once absorbed mirex is readily stored and poorly excreted.

Ivie et al. (1974) fed rats diets containing 0.3, 3 or 30 ppm mirex for up to 16 months and reported that mirex was rapidly absorbed and retained in tissues in a dose-related manner. Mirex concentrations in tissues steadily increased during exposure and no plateau was reached. One half or less of the dose was eliminated after 10 months.

Other authors have reported data indicating mirex absorption >50%. Gibson et al. (1972) gave rats single oral doses of 0.2 mg/kg radiolabeled mirex in corn oil, and found that 18% of the total radioactivity was eliminated in 7 days, with fecal elimination in the first 48 hours accounting for 2% of the total elimination. Chambers et al. (1982) gave rats single oral doses of 38 µg mirex. Fecal elimination in the first 2 days was 21-29% of the total dose and probably represented unabsorbed mirex. Total fecal elimination in 2 weeks was 25-31% of the total dose. Urinary elimination was <1% in 2 weeks. These data indicate a mirex absorption rate of 70-80%. Byrd et al. (1982) used pharmacokinetic data from oral and intravenous studies to construct a pharmacokinetic model for mirex in rats. This model indicated that average absorption of a 1 mg/kg oral dose was 69%.

2.2. INHALATION

Pertinent data regarding respiratory absorption of mirex could not be located in the available literature.

3. TOXICITY IN HUMANS AND EXPERIMENTAL ANIMALS

3.1. SUBCHRONIC

3.1.1. Oral. There were several studies available concerning the subchronic oral toxicity of mirex in laboratory animals. Most of these are summarized in Table 3-1. The most common effects of subchronic mirex intoxication were weight loss and increased relative liver weight and reproductive failure (NAS/NRC. 1978).

Because of its highly bioaccumulative nature, very low doses of mirex can be toxic in extended exposures. Hayes (1967) proposed a "chronicity factor," defined as the single dose LD_{50} divided by the 90 dose LD_{50}, to reflect cumulative effects of toxicants. Gaines and Kimbrough (1970) reported a single dose LD_{50} of 365 mg/kg and a 90 dose LD_{50} of 6 mg/kg/day. The resulting chronicity factor of 60.8 was the highest factor reported for any pesticide, including DDT (5.6) and dieldrin (12.8) (U.S. EPA, 1980).

3.1.2. Inhalation. Pertinent data concerning subchronic toxicity of inhaled mirex could not be located in the available literature.

3.2. CHRONIC

3.2.1. Oral. Monitoring data indicate that humans are exposed to mirex through consumption of seafood, fish, game and mammals as well as mothers milk (NAS/NRC, 1978); however, toxic effects in humans have not been reported. Since mirex is strongly bioaccumulated and very slowly eliminated, prolonged low level exposures may lead to significant body burdens. In general, for chemicals exhibiting these characteristics, stressful conditions such as weight loss or illness, resulting in depletion of fat reserves may result in mobilization and redistribution of mirex, possibly leading to toxic concentrations in the brain, liver or kidney (Geyer et al., 1980).

TABLE 3-1

Summary of Subchronic Oral Toxicity Data for Mirex

Species/Strain	Number/Sex	Dose, Vehicle	Duration	Effects	Reference
Rats/Sherman	10/sex/group	0, 1, 5, 25 ppm	166 days	Histological effects in liver, increased relative liver weight at 25 ppm; slight hepatocellular hypertrophy in males at 1 ppm and females at 5 ppm	Gaines and Kimbrough, 1970
Rats/CR	10/sex/group	0, 5, 20, 80, 320 or 1280 ppm diet	≤90 days	Vacuolation and swelling at liver cells, increased relative liver weight at ≥80 ppm; mortality at high dose; no adverse effects at <80 ppm	Larson et al., 1979
Rats/Sprague-Dawley	NR	5 or 30 ppm diet	8 or 12 months	Minimal proliferation of smooth endoplasmic reticulum at 5 ppm	Fulfs et al., 1977
Rats/Sprague-Dawley	NR	0, 5, 50 ppm diet	28 days	Minimal changes in hepatocytes and thyroid at 5 ppm, more pronounced at 50 ppm	Singh et al., 1979, 1985
Rats/Sprague-Dawley	NR/M	0.5, 5, 50, 75 ppm diet	28 days	Increased relative liver weights at ≥5 ppm; histolopathological effects on liver and thyroid at 75 ppm	Yarbrough et al., 1981
Rats/NR	NR	1.78, 17.8 ppm diet	40 days	No behavioral effects	Thorne et al., 1978
Rats/Sprague-Dawley	NR/M,F	10-50 ppm, oral	4 weeks	Decreased levels of some liver enzymes	Abston and Yarbrough, 1976
Rats/Sprague-Dawley	3-5/M	20 or 100 ppm diet	15 days	Dose-related hepatobiliary dysfunction	Curtis and Hoyt, 1984
Rats/Sprague-Dawley	6/M	0.25, 1, 5 ppm diet	2 weeks	Liver enzyme induction at 1 and 5 ppm, no effect at 0.25 ppm	Iverson, 1976
Mice/CD-1	NR/M	60 ppm diet	14 days, observed for additional 14 weeks	Increased relative liver weight	Byard and Pittman, 1975
Mice/B6C3F1	NR	15 ppm diet	8 weeks	Increased mortality and liver necrosis	Hayes and Abraham, 1979
Mice/NR	NR	1-90 ppm diet	5 days-13 months	Slight increase in relative liver weight at 1 ppm; mortality at doses ≥5 ppm; biochemical effects at all doses	Byard et al., 1974, 1975

Species/Strain	Number/Sex	Dose, Vehicle	Duration	Effects	Reference
Mice/CD-1	100/sex/group	1, 5, 15 or 30 ppm diet	≤18 months	Minimal hepatic centrilobular hypertrophy at 1 ppm.	Fulfs et al., 1977
Dogs/beagle	2/sex/group	4, 20, 100 ppm diet	13 weeks	Mortality, reduced weight gain, increased relative liver weights, decreased relative spleen weights at 100 ppm; no effect at 4 and 20 ppm	Larson et al., 1979
Monkeys/rhesus	NR	0.25 or 1 mg/kg/day in corn oil	≤26 months	"Slight effects" at 1 mg/kg/day (monkeys less sensitive than rats or mice in same study).	Fulfs et al., 1977

NR = Not reported

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Carcinogenicity was the primary focus of the three animal studies involving chronic exposure to mirex. Therefore, these studies are discussed in more detail in Chapter 4.

In reviewing data from the Ulland et al. (1973) chronic study, Reuber (1977) reported that rats exposed to diets containing 50 or 100 ppm mirex for 2 years had severe liver and kidney necrosis and chronic nephritis.

The NTP (1987) conducted a chronic bioassay with F344/N rats to determine possible carcinogenicity of mirex (see Chapter 4). Groups of 52 F344/N rats of each sex were fed diets containing 0, 0.1, 1.0, 10, 25 or 50 ppm mirex for 104 weeks and sacrificed 8-10 weeks later. During the first 6 months of the 2-year study, because of good survival and absence of observable toxic effects in female rats, additional groups (termed second study) of 52 F344/N female rats were started at dietary concentrations of 0, 50 and 100 ppm mirex.

Mean body weights of male rats that received 25 or 50 ppm mirex were 5-18% lower than those of the controls throughout most of the study; mean body weights of female rats that received 50-100 ppm mirex were 4-18% lower than those of the controls after week 40. (Feed consumption by dosed male rats was 83-91% that of controls, and that by dosed female rats was 86-99% that of controls. At the end of the study, the survival of male rats that received 25 or 50 ppm mirex was lower than that of controls (controls, 44/52; 25 ppm, 19/52; 50 ppm, 15/52).

The most notable effects were observed in the livers of both male and female rats. Fatty metamorphosis, cytomegaly, angiectasis (males only) and necrosis of the liver were observed at increased incidence in dosed rats. A significant increase in the incidence of hyperplasia of the transitional epithelium of the kidney pelvis was also observed in male rats (controls, 0/51; 0.1 ppm, 2/51; 1 ppm, 2/52; 10 ppm, 5/52; 25 ppm, 14/51; 50 ppm, 9/52).

3.2.2. Inhalation. Chronic inhalation experiments with mirex could not be located in the available literature.

3.3. TERATOGENICITY AND OTHER REPRODUCTIVE EFFECTS

3.3.1. Oral. There are several studies available concerning possible teratogenic and reproductive effects of mirex. These are summarized in Table 3-2. Mirex has been found to cause abnormalities including scoliosis, cleft palate, cataracts and heart defects (NAS/NRC, 1978). Maternal toxicity and reduced survival of offspring were also evident in some of these studies. Reproductive effects of mirex include reductions in fertility and litter size, decreased birth weight and reduced survival of offspring.

Fetal edema is commonly reported in mirex reproductive studies (Buelke-Sam et al., 1983; Byrd et al., 1980; Chernoff et al., 1979a; Kavlock et al., 1982). Disruption of maternal blood flow appears to be the mechanism underlying this and possibly other observed reproductive and teratogenic effects of mirex. Buelke-Sam et al. (1983) found that maternal visceral blood flow, particularly uterine and conceptus blood flow, was markedly reduced in mirex-treated rats. These authors proposed that the resulting hypoxia during organogenesis was responsible for reduced fetal weights, fetal edema and prenatal death, as well as toxic effects on maternal organs.

Mirex also causes cardiac defects, including dysrhythmias, in fetal and newborn rats (Grabowski, 1982, 1983a,b; Grabowski and Payne, 1980). This appears to be the most sensitive effect of mirex in reproductive studies, with no NOEL determined in studies in which doses as low as 0.1 mg/kg/day for 6-8 days during organogenesis or organ development were used (Grabowski, 1983a,b). These effects were not accompanied by obvious abnormalities. Some of the dysrhythmias were transient and benign, but others were fatal.

TABLE 3-2

Summary Table for Teratogenicity and Other Reproductive Effects*

Species/Strain	Number/Sex	Dose/Duration	Effect	Reference
Rat/Wistar (175-200 g)	20/F	12.5 mg/kg in corn oil by gavage on gestation days 6-15	Reduced fetal survival and fetal weight	Khera et al., 1976
Rat/Wistar	20/F/dose	12.5 and 6.0 mg/kg on gestation days 6-15	Maternal toxicity, fetal visceral anomalies	Khera et al., 1976
Rat/Wistar	10/F/dose	3.0 and 1.5 mg/kg on gestation days 6-15	No fetal or maternal effects	Khera et al., 1976
Rat/Wistar	20/M/dose	6.0 mg/kg/day in corn oil by gavage for 10 days followed by 14 consecutive (5-day) mating trials	Reduction in body weight gain; decreased incidence of pregnancies in first trial (postireatment days 0-5), but no dominant lethal effect	Khera et al., 1976
Rat/Wistar	20/M/dose	3.0 or 1.5 mg/kg/day as above	No observed adverse effects	Khera et al., 1976
Rat/CD	120 litters	38, 19 and 9.5 mg/kg/day in corn oil by gavage on gestation days 7-16	Increased numbers of dead and edematous fetuses, enlarged cerebral ventricles, undescended testes, reduced caudal ossification; dose-dependent maternal toxicity.	Chernoff et al., 1979a
Rat/CD	120 litters	7 and 5 mg/kg/day	No significant fetal effects; no information on maternal toxicity	Chernoff et al., 1979a
Rat/CD	6 litters/ dose	6 and 12 mg/kg/day on gestation days 7-16	Edematous fetuses, reduced fetal weights	Kavlock et al., 1982
Rat/CD	NR	10 mg/kg/day on gestation days 5-14	Increased prenatal mortality	Byrd et al., 1980
Rat/CD	NR	10 mg/kg/day on gestation days 5-14	Increased prenatal mortality (inversely correlated with maternal cardiac output); edema and reduced fetal weight; decreased blood flow to liver, kidney and adrenals of mothers	Byrd et al., 1980
Rat/Sherman	NR/F	5 mg/kg/day in corn oil by gavage on days 1-5 postpartum	Histopathological effects in lenses of pups.	Scotti et al., 1981
Rat/Long-Evans	NR/F	6 mg/kg/day on gestation days 8-15	Cataracts in offspring	Rogers et al., 1984
Rat/CD	6-7/F	10 mg/kg/day various intervals during gestation	Maternal toxicity; reduced fetal viability, fetal weight, edema.	Buelke-Sam et al., 1983

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TABLE 3-2 (cont.)

Species/Strain	Number/Sex	Dose/Duration	Effect	Reference
Rat/Long-Evans	205 fetuses	5, 6, 7 or 20 mg/kg/day in peanut oil by gavage on gestation days 8-15	Edema, tachycardia, heart blocks, and arrhythmias in fetuses	Grabowski and Payne, 1980
Rat/NR	NR	6 mg/kg in oil by gavage on gestation days 8-15	Depression of serum protein and colloid osmotic pressure in fetuses on days 16-21 of gestation	Grabowski and Payne, 1980
Rat/NR	NR	6 mg/kg in oil by gavage	Increased stillbirths; lower heart rates, survival rates; and heart blocks in offspring	Grabowski and Payne, 1980
Rat/NR	NR	1 mg/kg/day on gestation days 15-21	High rate of stillbirths and postnatal mortality, heart blocks and cataracts.	Grabowski, 1982
Rat/CD	NR	10 mg/kg/day on gestation days 5-14	Increased mortality in utero, increased late resorptions, similar but less pronounced effects at same dosage given on gestation days 6-15	Byrd et al., 1980
Rat/Long-Evans and Sherman	NR	1-10 mg/kg/day on days 1-4 postpartum	Dose-related incidence of cataracts in pups.	Chernoff et al., 1976
Rat/CD	NR	25 ppm in diet on gestation day 4-46 days postpartum	Induction of N-demethylase rates to nearly 7 times controls; placental and lactogenic transfer of chemical to offspring	Stevens et al., 1979
Rat/Sherman	10/f	25 ppm in diet, bred after 45 days and continued on treatment through lactation	Reduction in litter size; lower survival to weaning; and cataracts in offspring	Gaines and Kimbrough, 1970
Rat/Sherman	10/f	25 ppm in diet, bred after 102 days and continued on treatment through lactation	Reduction in number of litters; reduced survival and cataracts in offspring	Gaines and Kimbrough, 1970
Rat/CD	13-24 litters	25 ppm in diet on gestation day 4-45 days postpartum and pups cross-fostered with controls	Increased stillbirths following prenatal exposures; depressed growth and cataracts following postnatal exposures; reduced viability following prenatal or postnatal exposure; lactogenic and placental transfer	Chernoff et al., 1979b
Rat/Sherman	10/M	25 ppm in diet for 45-102 days	No reproductive effects when bred to controls on days 45 and 102 of treatment	Gaines and Kimbrough, 1970
Rat/NR	NR	0.25, 0.50 mg/kg/day in oil by gavage on gestation days 15-21	Cardiac dysrhythmias, increased perinatal death rate	Grabowski, 1983a
Rat/Long-Evans	NR	0.1-0.5 mg/kg/day in peanut oil by gavage on days 15.5-21.5 of gestation	Dysrhythmias and first degree heart block in offspring within 5 minutes to 5 days after birth	Grabowski, 1983b

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TABLE 3-2 (cont.)

Species/Strain	Number/Sex	Dose/Duration	Effect	Reference
Rat/Long-Evans	NR	10 mg/kg/day on days 1-4 post-partum	Cataracts in 71% of litters	Rogers and Grahowski, 1984
Rat/Sherman	10/F	5 ppm in diet for ≥4 months	No reproductive effects when bred to untreated controls	Gaines and Kimbrough, 1970
Rat/Sherman	litters from 10 females	25 ppm (dams) in diet; off-spring of dams treated 49 days and transferred at birth to untreated foster dams	No reproductive effects	Gaines and Kimbrough, 1970
Rat/Sherman strain	litters from 10 females	25 ppm (dams) in diet; exposed postpartum only to treated dams until weaned	Lower survival rates and cataracts	Gaines and Kimbrough, 1970
Rat/Sprague-Dawley	15/M 20/F	5, 10, 20, 40 ppm diet for 91 days prior to mating and throughout gestation and lactation	Decreased litter size; liver and thyroid histo-pathology in dams and pups.	Chu et al., 1981
Goat/NR	5/M 5/F	1 mg/kg/day for 61 weeks followed by 10 mg/kg/day for 4 weeks (females only)	No observed adverse effects; normal body weight and fertility; normal offspring	Smrek et al., 1977
	5/F	1 mg/kg/day for first 18 weeks postpartum followed by 10 mg/kg/day for 4 weeks	No observed adverse effects; normal body weight and fertility; normal offpsring	Smrek et al., 1977
Mice/BALB/C	102/M 102/F	5 ppm diet for 30 days, mated and continued on diet for additional 90 days	Increased prenatal mortality, decreased fertility and fecundity.	Ware and Good, 1967
Mice/CD-1	24/F	7.5 mg/kg/day by gavage on days 8-14 of gestation	Reduced weight of offspring and reduced number born alive	Chernoff and Kavlock, 1982

*Source: NAS/NRC, 1978

NR = Not reported

00944

04/25/87

A third commonly reported effect of mirex in reproduction/teratogenicity studies is formation of cataracts in offspring (Chernoff et al., 1976, 1979b; Chu et al., 1981; Gaines and Kimbrough, 1970; Grabowski, 1982; Rogers et al., 1984; Rogers and Grabowski, 1984). Cataract formation has been induced by both prenatal and perinatal exposure to mirex.

3.3.2. Inhalation. Reports of teratogenicity or reproductive effect studies with mirex by inhalation exposure could not be located in the available literature.

3.4. TOXICANT INTERACTIONS

There were several studies available concerning the effects of mirex on the toxicity of other compounds. Mirex reportedly had no effect on the hepatotoxicity caused by chloroform (Bell and Mehendale, 1985; Cianflone et al., 1979, 1980; Curtis and Mehendale, 1980; Curtis et al., 1979, 1981; Hewett et al., 1978). Abraham et al. (1974) fed mice diets containing PCBs or mirex or both, and found that the most severe toxic effects occurred in mice receiving a combination of PCB and mirex; however, it was not reported if the effects appeared to be additive or synergistic.

4. CARCINOGENICITY

4.1. HUMAN DATA

The only epidemiological study available of cancer incidence in relation to mirex exposure was that concerning residents of the Love Canal area in New York. There was no evidence of higher cancer rates associated with residence in this area (Janerich et al., 1981).

4.2. BIOASSAYS

4.2.1. Oral. Relevant data from three chronic oral carcinogenicity bioassays in animals are summarized in Table 4-1.

Innes et al. (1969) tested an unspecified commercial mirex formulation in two hybrid strains of mice, (C57Bl/6xC3H/AnF)F1 and (C57Bl/6xAKR)F1. Treated mice (18/sex/strain) initially received gavage doses of 10 mg/kg/day on days 7-28 of age, then received a diet containing 26 ppm mirex for 18 months, approximating the MTD. All treated mice died before 18 months. Tumorigenicity was evaluated by the authors based on magnitude of relative risk, comparing tumor incidence in treated mice with controls. A separate analysis using the Mantel-Haenszel procedure was performed for hepatomas, pulmonary tumors, lymphomas and total mice with tumors. Mirex caused a significant ($p<0.01$) increase in hepatomas in both strains of treated mice (29/65; 65 of 72 animals were necropsied) compared with controls (14/338). The hepatoma classification included both hepatomas and carcinomas. Six known carcinogens (urethan, amitrol, aramite, dihydrosafrole, isosafrole and safrole) were used as positive controls in this study and were clearly tumorigenic. By comparison with the average response of the seven positive controls (number of mice with hepatomas), mirex had a relative risk of 0.945 across both strains and sexes, meaning that mirex possessed ~95% of the carcinogenic potency of the known carcinogens tested in this study (Innes et

TABLE 4-1

Summary Table for Carcinogenicity Studies on Mirex

Species/Strain	Number, Sex	Dose Schedule	Duration of Treatment (months)	Duration of Observation (months)	Tumor Incidence[a]	Tumor Type	Reference
Mouse/(C57Bl/6x C3H/Anf)F1, (C57Bl/6xAKR)F1	18,M 18,F 18,M 18,F	10 mg/kg/day, days 7-28 (stomach tube) followed by 26 ppm in diet until 18 months of age	18 18 	18 18 	6/18[b] 8/18 5/18[c] 10/18[c]	Hepatoma Hepatoma Hepatoma Hepatoma	Innes et al., 1969
Mouse/combined strains	36,M 36,F	10 mg/kg/day, days 7-28 (stomach tube) followed by 26 ppm in diet until 18 months of age	18 	18 	11/36[c] 18/36[c]	Hepatoma Hepatoma	
Mouse/(C57Bl/6x C3H/Anf)F1	79,M 87,F	control control	NA NA	-18 -18	8/79 0/87	Hepatoma Hepatoma	
(C57Bl/6xAKR)F1	90,M 82,M	control control	NA NA	-18 -18	5/90 1/82	Hepatoma Hepatoma	
Mouse/combined strains	169,M 169,F	control control	NA NA	-18 -18	13/169 1/169	Hepatoma Hepatoma	
Rat/Charles River CD	26,M	80 ppm for 10 weeks 100 ppm for 15.5 months	18	24	4/26	Hepatocellular carcinoma	Ulland et al., 1977
	26,F	80 ppm for 10 weeks 100 ppm for 15.5 months	18	24	7/26[b] 1/26	Liver, neoplastic nodule Hepatocellular carcinoma	
	26,M	40 ppm for 10 weeks 50 ppm for 15.5 months	18	24	4/26 1/26	Liver, neoplastic nodule Hepatocellular carcinoma	
	26,F	40 ppm for 10 weeks 50 ppm for 15.5 months	18	24	2/26	Liver, neoplastic nodule Hepatocellular carcinoma	
	20,M	0 ppm	18	24	4/26 0/26	Liver, neoplastic nodule Hepatocellular carcinoma	
	20,F	0 ppm	18	24	0/26 0/26	Liver, neoplastic nodule Hepatocellular carcinoma	

TABLE 4-1 (cont.)

Species/Strain	Number, Sex	Dose Schedule	Duration of Treatment (weeks)	Duration of Observation (weeks)	Tumor Incidence[a]	Tumor Type	Reference
Rat/Fischer 344/N	52,M	0 ppm	104	112-113	3/52 10/51	Liver, neoplastic nodule Pheochromocytomas/malignant pheochromocytoma at adrenal gland	NTP, 1987
	52,M	0.1 ppm	104	112-113	5/52 7/52	Liver, neoplastic nodule adrenal gland	
	52,M	1 ppm	104	112-113	5/52 13/52	Liver, neoplastic nodule adrenal gland	
	52,M	10 ppm	104	112-113	14/52 12/52	Liver, neoplastic nodule adrenal gland	
	52,M	25 ppm	104	112-113	15/52 18/51	Liver, neoplastic nodule adrenal gland	
	52,M	50 ppm	104	112-113	26/52 20/51	Liver, neoplastic nodule adrenal gland	
	52,F (first study)	0 ppm	104	112-113	8/52	Mononuclear cell leukemia	
	52,F	0.1 ppm	104	112-113	8/52	Leukemia	
	52,F	1 ppm	104	112-113	11/52	Leukemia	
	52,F	10 ppm	104	112-113	14/52	Leukemia	
	52,F	25 ppm	104	112-113	18/52	Leukemia	
	52,F	50 ppm	104	112-113	18/52	Leukemia	

TABLE 4-1 (cont.)

Species/Strain	Number, Sex	Dose Schedule	Duration of Treatment (weeks)	Duration of Observation (weeks)	Tumor Incidence[a]	Tumor Type	Reference
Rat/Fischer 344/N	52,F (second study)	0 ppm	104	112-113	2/52 6/52	Liver, neoplastic leukemia	NTP, 1987
	52,F	50 ppm	104	112-113	23/52 9/52	Liver, neoplastic leukemia	
	52,F	100 ppm	104	112-113	30/52 14/52	Liver, neoplastic leukemia	

[a]Denominators based on total animals on test, unadjusted for survival

[b]Significant at $p<0.05$

[c]Significant at $p<0.01$

NA = Not applicable

04/30/87

00944

al., 1969). The female mice of both strains, when compared with female positive controls of the respective strains, had relative risks for hepatomas of 1.07 and 2.9 for the (C57B1/6 x C3H/Anf) F1 and (C57B1/6 x AKR) F1, respectively, while the males had relative risks for hepatomas of 0.38 and 0.7, respectively.

Ulland et al. (1973, 1977) fed groups of 26 male and 26 female Charles River CD rats diets containing mirex (99% purity) at concentrations of 50 and 100 ppm for 18 months. Untreated controls and positive controls treated with a known carcinogen (2-AAF) were also included. There was a treatment-related decrease in survival. In the original evaluation, mirex was reported not to be carcinogenic; however, a reevaluation using guidelines for the classification of liver tumors developed at an NCI workshop indicated that mirex was carcinogenic (Ulland et al., 1973). A summary of this controversy was presented by Ulland et al. (1977). Major points from their discussion are summarized below.

The test animals showed a wide spectrum of neoplasms which, except for liver lesions, showed little correlation with mirex dosage. Therefore, the relationship between mirex exposure and the development of lesions at other sites could not be established. There was a high incidence of tumors, regardless of sex or dose, but no statistically significant differences were noted except for tumors of the liver (neoplastic nodules). One carcinoma was detected in the low-dose group, five in the high-dose group and none in the control group. The difference in this parameter between test animals and controls was not significantly different. Only the observation of seven neoplastic nodules of the liver in the high-dose (100 ppm) male rats was significant at $p \leq 0.05$. The authors did state, however, that this type of neoplastic nodule has been shown to progress to hepatocellular carcinoma in

studies of other carcinogens. In addition, the absence of neoplastic nodules among controls and the fact that this type of lesion is characteristic of early response to known carcinogens also suggests carcinogenic activity. According to the authors, to call such nodules merely hyperplastic belies their neoplastic nature and malignant potential.

In the NTP (1987) carcinogenicity bioassay, currently available in draft form, groups of 52 F344/N rats of each sex were fed diets containing 0, 0.1, 1.0, 10, 25 or 50 ppm mirex for 104 weeks and sacrificed 8-10 weeks later. During the first 6 months of the 2-year study, because of good survival and the absence of observable toxic effects in female rats, additional groups (termed second study) of 52 F344/N female rats were started at dietary concentrations of 0, 50 and 100 ppm mirex. The average amount of mirex consumed per day in the first studies was ~0.007, 0.07, 0.7, 1.9 and 3.8 mg mirex/kg bw, respectively, for the 0.1, 1, 10, 25 and 50 ppm groups of male and female rats. For the second study in female rats the feed consumption data are incomplete; however, based on the feed consumption data for the first study in female rats, average estimated mirex doses would have been 3.8 and 7.7 mg/kg for the 50 and 100 ppm groups, respectively.

In male rats, there was a dose-related increase in hepatocellular neoplastic nodules (controls, 3/52; 0.1 ppm, 5/52; 1 ppm, 5/52; 10 ppm, 14/52; 25 ppm, 15/52; 50 ppm, 26/52) and the 10, 25 and 50 ppm groups were significantly greater than controls. In female rats (second study), the incidence of hepatocellular neoplastic nodules was dose-related and significantly greater than controls (controls, 2/52; 50 ppm, 23/52; 100 ppm, 30/52).

In the first female rat study the control incidence rate was elevated as compared with both historical controls and the control group females in the second study, precluding pooling of the data from the first and second study for hepatocellular neoplastic nodules. In addition, any potential compound-related incidence rate could have been obscured by the elevated control incidence rate in the first study.

The incidence of pheochromocytomas/malignant pheochromocytomas (combined) of the adrenal gland occurred with a positive trend ($p<0.001$, Cochran-Armitage test) in male rats (controls, 10/51; 0.1 ppm, 7/52; 1 ppm, 13/52; 10 ppm, 12/52; 25 ppm, 18/51; 50 ppm, 20/51). The incidences in the 25 and 50 ppm male rats were significantly greater than controls ($p<0.005$, Fischer Exact test). In addition, there was a positive trend with dose for transitional cell papillomas of the kidney in male rats. However, in the draft report the authors expressed reservations concerning the biological significance and ability of this tumor type to progress.

In both the first and second studies in female rats, the incidence of mononuclear cell leukemia showed a dose-related increase (first study: controls, 8/52; 0.1 ppm, 8/52; 1 ppm, 11/52; 10 ppm, 14/52; 25 ppm, 18/52; 50 ppm, 18/52; second study: controls, 6/52; 50 ppm, 9/52; 100 ppm, 14/52). When the data from both studies are combined, the incidences are significantly increased in the 10, 25, 50 and 100 ppm groups.

The authors concluded that mirex is clearly carcinogenic in both male and female F344/N rats as indicated by marked increased incidences of benign neoplastic nodules of the liver in both males and females, as well as incidences of mononuclear cell leukemia in females and increased incidences of pheochromocytomas of the adrenal gland in males.

4.2.2. Inhalation. Carcinogenicity bioassays in which mirex was administered by inhalation could not be located in the available literature.

4.3. OTHER RELEVANT DATA

Abraham et al. (1983) examined ploidy patterns in livers of male Sprague-Dawley rats receiving 100 ppm mirex in the diet for 13 months. The distribution of diploid and tetraploid nuclei in nodular (e.g., adenomas and carcinomas) and nonnodular areas was analyzed. Mirex disturbed the usual distribution of nodular areas within the ploidy classes, selectively reducing the number of tetraploid cells. This effect is consistent with the nature of liver tumors in rats, the greatest effect occuring in hepatocellular carcinomas.

There is relatively little information available concerning mutagenicity of mirex. Hallet et al. (1978), Schoeny et al. (1979) and NTP (1987) found that mirex was not mutagenic to five strains of Salmonella typhimurium in standard Ames tests with or without mammalian activating systems. Mirex did not induce either sister chromatid exchanges or chromosomal aberrations in Chinese hamster ovary cells in the presence or absence of a mammalian activating system.

4.4. WEIGHT OF EVIDENCE

IARC (1979) reviewed the available evidence concerning mirex carcinogenicity and concluded that there was "sufficient evidence that mirex is carcinogenic in mice and rats." Human data were inadequate for evaluation, and IARC (1979) concluded that it would be reasonable to regard mirex as if it presented a carcinogenic risk for humans. Using the U.S. EPA (1986) guidelines, mirex would be classified in EPA Group B2, probable human carcinogen, on the basis of sufficient evidence from animal studies (multiple experiments in different species) and inadequate evidence from human studies.

5. REGULATORY STANDARDS AND CRITERIA

The following tolerances for residues of mirex on raw agricultural commodities have been established (Code of Federal Regulations, 1982; U.S. EPA, 1983a): 0.1 ppm (negligible residue) in the fat of meat from cattle, goats, hogs, horses and sheep; 0.1 ppm in milk fat, reflecting negligible residues in milk; 0.1 ppm (negligible residue) in eggs; 0.01 ppm (negligible residue) in or on all raw agricultural commodities, exclusive of those mentioned above.

U.S. EPA (1976) recommended a water quality criterion of 0.001 µg/ℓ for the protection of aquatic life. This value was derived by applying a safety factor of 0.01 to the lowest concentration affecting several species of aquatic crustaceans.

6. RISK ASSESSMENT

6.1. ACCEPTABLE INTAKE SUBCHRONIC (AIS)

Because of its carcinogenicity, no oral or inhalation AIS values can be calculated for mirex.

6.2. ACCEPTABLE INTAKE CHRONIC (AIC)

Because of its carcinogenicity, no oral or inhalation AIC values can be calculated for mirex.

6.3. CARCINOGENIC POTENCY (q_1*)

6.3.1. Oral. Although there are no epidemiological studies available that are useful for assessing carcinogenic risk of mirex to humans, there are three animal studies available that indicate that mirex is carcinogenic (Innes et al., 1969; Ulland et al., 1973, 1977; NTP, 1987).

Innes et al. (1969) found that mirex (26 ppm diet) caused a significant increase in hepatomas in male and female strain (C57Bl/6xAKR)F1 mice ($p<0.01$) and in male strain (C57Bl/6xC3H/Anf)F1 mice ($p<0.05$).

Ulland et al. (1977) reported that mirex caused a significant increase ($p<0.05$) in neoplastic nodules of the liver in male Charles River CD rats exposed to 80-100 ppm diet for 18 months. They noted that progression of these nodules to hepatocellular carcinomas was highly probable and therefore, these data are suggestive of mirex carcinogenicity.

Reporting inadequacies (both studies) and the controversy over tumor classification (Ulland, 1973, 1977), combined with only a single dose level and high mortality in the Innes et al. (1969) study, make these evaluations less than optimum for quantitative risk assessment.

A draft report of an NTP study not subject to these deficiencies is also available (NTP, 1987). In this study groups of 52 rats/sex/dose were fed diets containing 0, 0.1, 1.0, 10, 25 or 50 ppm mirex for 104 weeks and

sacrificed 8-10 weeks later. An additional study with female rats was included in which 52 female rats/dose were exposed through their diet to 0, 50 or 100 ppm mirex (second study).

In this NTP study, incidences of neoplastic liver nodules were increased in both male and female rats, without increases in hepatocellular carcinoma. Liver nodules are generally assumed to have the potential to progress to malignancy. In the first female rat study, concurrent control incidence of nodules was significantly elevated compared with both historic controls and concurrent controls from the second study.

The incidence of pheochromocytomas or combined pheochromocytomas and malignant pheochromocytomas of the adrenal gland showed a positive dose trend in males with the 25 and 50 ppm dose groups being significantly different from controls in pairwise comparisons.

Mononuclear cell leukemia showed positive dose-related trends in both studies with female rats. Pairwise comparisons showed that the 25 and 50 ppm groups were significantly different from the concurrent control in the first study and the 100 ppm group was elevated compared with the second study concurrent control. Since the control groups did not differ significantly, the data were pooled by NTP and an analysis of the pooled data indicated that the 10, 25, 50 and 100 ppm groups were significantly different from controls.

Potency estimates and associated parameters were developed using Global 82 (Howe and Crump, 1982) and are shown in Tables 6-1, 6-2 and 6-3. The cancer guidelines (U.S. EPA, 1986) suggest that in order to obtain a total estimate of carcinogenic risk animals with one or more tumor sites or types, of those types showing a significantly elevated incidence in response to

TABLE 6-1

Cancer Data Sheet for Derivation of q_1^*

Reference: NTP, 1987

Compound: mirex

Species, strain, sex: rats, Fischer F344/N, male

Route/vehicle: oral, diet

Length of exposure (le) = 104 weeks

Length of experiment (Le) = 104 weeks

Lifespan of animal (L) = 104 weeks

Body weight = 0.35 kg (estimated from graphic data provided by investigators)

Tumor site and type: liver neoplastic nodule, hepatocellular carcinoma, adrenal pheochromocytoma and malignant pheochromocytoma

Route, Vehicle: oral, diet

Experimental Doses or Exposures (ppm)	Transformed Dose[a] (mg/kg/day)	Incidence No. Responding/No. Tested
0	0	16/52
0.1	0.007	11/52
1	0.07	17/52
10	0.7	23/52
25	1.8	27/51[b]
50	3.8	35/52

[a]Estimated by the authors

[b]Adrenal not examined in one rat that did not have hepatocellular neoplastic nodule or hepatocellular carcinoma

Unadjusted q_1^* from study = 3.0895188×10^{-1} $(mg/kg/day)^{-1}$
Human q_1^* = 1.8068 $(mg/kg/day)^{-1}$

TABLE 6-2

Cancer Data Sheet for Derivation of q_1^*

Reference: NTP, 1987

Compound: mirex

Species, strain, sex: rats, Fischer F344/N, female

Route/vehicle: oral, diet

Length of exposure (le) = 104 weeks

Length of experiment (Le) = 104 weeks

Lifespan of animal (L) = 104 weeks

Body weight = 0.24 kg (estimated from graphic data provided by investigators)

Tumor site and type: liver neoplastic nodule, hepatocellular carcinoma and leukemia

Route, Vehicle: oral, diet

Experimental Doses or Exposures (ppm)	Transformed Dose† (mg/kg/day)	Incidence No. Responding/No. Tested
0	0	17/52
0.1	0.007	13/52
1	0.08	13/52
10	0.7	18/52
25	2.0	22/52
50	3.9	21/52

†Estimated by the authors

Unadjusted q_1^* from study = 1.1854367×10^{-1} $(mg/kg/day)^{-1}$
Human q_1^* = 7.8615×10^{-1} $(mg/kg/day)^{-1}$

TABLE 6-3

Cancer Data Sheet for Derivation of q_1^*

Reference: NTP, 1987

Compound: mirex

Species, strain, sex: rats, Fischer F344/N, female, study #2

Route/vehicle: oral, diet

Length of exposure (le) = 104 weeks

Length of experiment (Le) = 104 weeks

Lifespan of animal (L) = 104 weeks

Body weight = 0.22 kg (estimated from graphic data provided by investigators)

Tumor site and type: liver neoplastic nodule, hepatocellular carcinoma and leukemia

Route, Vehicle: oral, diet

Experimental Doses or Exposures (ppm)	Transformed Dose† (mg/kg/day)	Incidence No. Responding/No. Tested
0	0	7/52
50	3.9	25/52
100	7.7	37/52

†Estimated by the authors

Unadjusted q_1^* from study = 1.7918064×10^{-1} $(mg/kg/day)^{-1}$
Human q_1^* = 1.2235 $(mg/kg/day)^{-1}$

treatment, should be pooled and the pooled estimates utilized for extrapolation. The guidelines also state that benign and malignant tumors should be combined unless the benign tumors are not considered to have the potential to progress to the associated malignancy.

Pooled counts were developed using the individual animal data appended to the NTP (1987) report. For male rats any animal having a diagnosed liver neoplastic nodule, hepatocellular carcinoma, adrenal pheochromocytoma or malignant pheochromocytoma was counted. For female rats for each study, any animal showing a diagnosed hepatic neoplastic nodule, hepatocellular carcinoma or leukemia was counted. The resulting human q_1^*s were 1.8, 0.8 and 1.2 $(mg/kg/day)^{-1}$ for the males, first study females and second study females, respectively.

The estimate of 1.8 $(mg/kg/day)^{-1}$ is chosen to represent the carcinogenic potency of mirex. It should be noted that the potency estimate includes benign tumor counts for two endpoints (liver and adrenal) based on their presumed potential to progress. It should also be noted that this estimate does not take into consideration the increased mortality rate seen in the two highest dose groups. This increase in intercurrent mortality could have resulted in fewer animals in these groups surviving to develop tumors. While the 1986 cancer guidelines suggest correction for intercurrent mortality, this correction cannot be performed without access to individual animal data on mortality. While NTP provides estimates of tumor incidence that take mortality into account, these estimates are for individual tumor sites rather than the pooled site estimates suggested by the guidelines. Potencies could be estimated based upon summed site-specific estimates; however, this would overestimate risk when animals exhibited more than one tumor type. With the high tumor incidences observed in this study this consideration could result in a significant overestimation of potency.

For purposes of comparison, these summed estimates were calculated for male rats. Summed q_1*s for individual sites corrected for mortality showed only a 3-fold increase over the pooled estimates. This small increase in the context of the high tumor incidence and error introduced by counting the same animal twice suggests that intercurrent mortality in this study had only a small affect on tumor incidence.

Review of the CBI file for mirex did not reveal any information that would affect this risk assessment.

6.3.2. Inhalation. There were no inhalation carcinogenicity data available for mirex, and therefore, no carcinogenic risk assessment can be performed.

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APPENDIX

Summary Table for Mirex*

Route	Species/ Strain/Sex	Experimental Exposure/Dose	Effect	q_1*
Oral	rat/ F344/N male	0, 0.1, 1, 10, 25, or 50 ppm in the diet	liver neoplastic nodules, adrenal pheochromocytomas	1.8 $(mg/kg/day)^{-1}$

*Source: NTP, 1987